DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Alexandra Burtoft
Associate Program Director, Commercial Regulatory Affairs
Genentech, Inc.
1 DNA Way MS #241A
South San Francisco, CA 94080-4990

RE: NDA #021743
Tarceva® (erlotinib) tablets
MA #259

Dear Ms. Burtoft,

As part of its monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the Food and Drug Administration (FDA) has reviewed the visual aids titled "Improving Outcomes in First-Line Advanced Pancreatic Cancer" (TAR0000319501) (Pancreatic Cancer Visual Aid) and "In Maintenance Therapy and Relapsed or Refractory NSCLC Extending Survival for Moments that Matter" (TAR0000086003) (NSCLC Visual Aid) for Tarceva® (erlotinib) tablets (Tarceva) submitted by Genentech, Inc. (Genentech) under cover of form 2253. These visual aids are misleading because they contain misleading efficacy claims, minimize the risks, and overstate the efficacy of Tarceva. As a result, these visual aids misbrand the drug in violation of the Federal Food, Drug and Cosmetic Act (the FD&C Act), 21 U.S.C 352(a). *Cf.* 21 CFR 202.1 (e)(5)(i); (e)(6)(i), (xviii); (e)(7)(i), (iii), & (viii).

Background[1]

Below are the indications and summary of the most serious and most common risks associated with the use of Tarceva. According to the FDA-approved Tarceva product labeling (PI):

- Tarceva monotherapy is indicated for the maintenance treatment of patients with locally advanced or metastatic non-small cell lung cancer whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.

- Tarceva monotherapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece(s) cited in this letter.

- Results from two, multicenter, placebo-controlled, randomized, Phase 3 trials conducted in first-line patients with locally advanced or metastatic NSCLC showed no clinical benefit with the concurrent administration of Tarceva with platinum-based chemotherapy (carboplatin and paclitaxel or gemcitabine and cisplatin) and its use is not recommended in that setting.

- Tarceva in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer.

Tarceva is associated with a number of serious risks, as detailed in the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the PI. These risks, many of which are associated with fatal events, include interstitial lung disease-like events, acute renal failure, renal insufficiency, hepatic failure, hepatorenal syndrome, gastrointestinal perforation, bullous and exfoliatve skin disorders, myocardial infarction/ischemia, microangiopathic hemolytic anemia, cerebrovascular accidents, corneal perforation/ulceration, International Normalized Ratio (INR) elevations, bleeding, and fetal harm. Caution is advised in patients with hepatic impairment.

The most common adverse events observed with Tarceva include rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, infection, vomiting, abdominal pain, weight decrease, infection, edema, pyrexia, constipation, bone pain, dyspnea, stomatitis, and myalgia.

Misleading Efficacy Claims/ Minimization of Risk

Promotional materials are misleading if they suggest that a drug is more effective or safer than has been demonstrated by substantial evidence or substantial clinical experience. The Pancreatic Cancer Visual Aid makes several claims that overstate the efficacy and minimize the risks of Tarceva. Page nine of the Pancreatic Cancer Visual Aid makes the following misleading claims:

- "Retrospective data suggest Tarceva-related rash is associated with a clinical benefit."

- "Based on a retrospective, exploratory analysis, a strong correlation was observed between the presence of rash and improved survival in the pivotal phase lll clinical trial.[2]"

These claims are presented in conjunction with a Kaplan-Meier (K-M) graph, titled "Overall Survival in Patients with Grade 2+ Rash,[3,[4]]" that compares overall survival (OS) in patients who developed a grade 2+ rash during treatment with Tarceva + gemcitabine to gemcitabine alone. The graph shows that patients taking Tarceva + gemcitabine who experienced a grade 2+ rash had a median OS of 10.7 months, compared to a median OS of 7.0 months in

[2] Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase lll trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2007;25(15):1960-1966.
[3] National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology: pancreatic carcinoma (version 1.2009). Fort Washington, PA: NCCN; 2009.
[4] National Comprehensive Cancer Network (NCCN). NCCN drugs and biologics compendium. Fort Washington, PA: NCCN; 2009.

patients taking gemcitabine alone. This presentation drastically overstates the efficacy of Tarceva by suggesting that in patients that develop grade 2+ rash, the addition of Tarceva to gemcitabine provides an additional 3.7 month OS benefit, and that these patients may have a median OS of 10.7 months. According to the PI, the addition of Tarceva to gemcitabine increased survival by ~12 days (6.4 months vs 6.0 months) in the indicated patient population. Therefore, this presentation misleadingly overstates the efficacy of Tarceva. Moreover, the development of rash and its correlation with OS were not pre-specified endpoints in the pivotal study. The data and subsequent claims presented in this sales aid were derived from a retrospective, exploratory subgroup analysis that does not provide substantial evidence to support the efficacy claims cited above.

Finally, this presentation minimizes the risks of Tarceva by portraying the adverse reaction of "rash" as an efficacy predictor and therefore a potential benefit to patients. According to the Tarceva PI, grade 3/4 rash was reported in 5% of patients in the Tarceva + gemcitabine arm and resulted in dose reductions in 2% of patients and study discontinuation in up to 1% of patients. We note that the page includes the statement: "These data do not support increasing the dosage of Tarceva to cause patients to develop rash," however, this statement does not mitigate the misleading impression conveyed by the presentation above.

Promotional materials are also false or misleading if they contain favorable data or conclusions in a way that suggest clinical significance when in fact no such clinical significance has been demonstrated. Several pages of the NSCLC Visual Aid include misleading claims such as:

> "Based on a retrospective exploratory analysis, the overall survival benefit in the ITT population extended to squamous cell carcinoma, a difficult-to treat disease[5,6,7]
>
> - Tarceva reduced the risk of death by 33% (HR=0.67; 95% CI=0.5-0.9; P=0.007; median: 5.6 months with Tarceva versus 3.6 months with placebo)" (page three)[5]
> - Overall survival benefit in the ITT population extended to squamous cell carcinoma[5]"
> - Tarceva significantly prolonged OS in squamous cell carcinoma, a difficult-to-treat disease[5,6,7]" (page 16)
>
> "Based on a retrospective exploratory analysis, with Tarceva in relapsed or refractory stage lllB/IV NSCLC
>
> - Overall survival benefit in the ITT population extended to adenocarcinoma[5]"
> - Tarceva significantly prolonged OS in adenocarcinoma[5]" (page 17)

The claims on page 16 are accompanied by a K-M graph titled "33% reduction in risk of death[5]" that compares OS in patients with squamous cell carcinoma in patients treated with Tarceva versus placebo. The graph depicts a 5.6 month median OS in the Tarceva arm

[5] Data on file, OSI Pharmaceuticals, LLC, an affiliate of Astellas Pharma US, Inc.
[6] Stitchcombe TE, Socinski MA, Considerations for second-line therapy of non-small cell lung cancer. *Oncologist*.2008;13(suppl 1):28-36.
[7] Hensing TA, Schell MJ, Lee JH, Socinski MA. Factors associated with the likelihood of receiving second-line therapy for advanced non-small cell lung cancer. *Lung Cancer*.2005;47(2):253-259.

compared to 3.6 months for placebo. Similarly, the claims on page 17 are presented in conjunction with a K-M curve titled "29% reduction in risk of death[5]" that compares OS in patients with adenocarcinoma. According to the graph, patients treated with Tarceva had a median OS of 7.8 months compared to 5.4 months for those in the placebo arm. These claims are based on retrospective exploratory analyses for subgroups of patients with adenocarcinoma and squamous cell carcinoma. These analyses do not provide substantial evidence to support these survival claims. Although tumor histology was collected along with other demographic characteristics during enrollment, the exploratory, retrospective analysis of efficacy in these patient subgroups is not supported due to the lack of adequate prospective statistical design. Therefore, the claims and presentations on these pages are misleading because they are not supported by substantial evidence or substantial clinical experience.

Overstatement of Efficacy

Promotional materials are misleading if they suggest that a drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. The front cover of the Pancreatic Cancer Visual Aid and the NSCLC Visual Aid include a prominent picture of an hourglass, labeled "Tarceva." The Tarceva hourglass is resting on its side, and inside the bottom half of the hourglass, an elderly person and a child are shown reading a book together. This image is presented in conjunction with one of the following claims (emphasis original):

- "Improving outcomes in first-line advanced pancreatic cancer
  - Extending survival for *moments that matter*"

- "In maintenance therapy and relapsed and refractory NSCLC
  - Extending survival for *moments that matter*"

In each case, because the Tarceva hourglass is positioned on its side, it appears that the sand in the upper half is no longer flowing down to the lower half where the cancer patient and child are located. This presentation strongly suggests that time is standing still for the cancer patient because of Tarceva therapy. This suggestion drastically overstates the overall survival benefit for patients. In the pivotal study that led to the approval of Tarceva for the treatment of advanced pancreatic cancer, the addition of Tarceva to gemcitabine resulted in a ~12 day increase in OS compared to the control arm (6.4 month OS in the Tarceva + gemcitabine versus 6.0 month OS for gemcitabine alone). In the pivotal study that led to the approval of Tarceva for maintenance therapy for NSCLC, the improvement in OS was one month (12 month OS in the Tarceva group versus 11 month OS in the placebo group). These improvements in OS do not support the implication that Tarceva can slow disease progression and greatly improve survival to the extent implied by the hourglass presentation. Moreover, the claim "extending survival *for moments that matter*" suggests a quality of life benefit for these patients, which was not demonstrated in the respective pivotal studies.

The NSCLC Visual Aid overstates the efficacy of Tarceva by including several claims about stable disease (SD) and disease control rate (complete response + partial response + SD). Specifically, page 19 includes the claim, "Significantly increased disease control rate in a

broad patient population.[8]" This claim is accompanied by a bar graph delineating stable disease, complete response, partial response, and the total response category of disease control rate. The graph presents SD as 35.1% in the Tarceva arm and 26.5% in the placebo arm. This claim misleadingly overstates the effectiveness of Tarceva by implying a clinical benefit of disease control that has not been demonstrated by substantial evidence or substantial clinical experience. As stated in the CLINICAL STUDIES section of the PI, "Study endpoints included overall survival, response rate, [which is comprised of complete response and partial response], and progression-free survival (PFS). Duration of response was also examined. The primary endpoint was survival." SD and disease control rate were not pre-specified endpoints in the pivotal study; therefore, claims that cite these efficacy parameters are not supported by substantial evidence or substantial clinical experience and overstate the efficacy of Tarceva.

Minimization of Risk

Promotional materials are misleading if they fail to present risk information with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of the drug. The Pancreatic Cancer and NSCLC Visual Aids use many techniques to emphasize and highlight the efficacy of Tarceva, including large, bolded headers, compelling visuals, bullets, and ample white space. However, several pages of both visual aids minimize the risks of Tarceva by including important risk information underneath an efficacy header. For example, the risk information at the bottom of page three of the Pancreatic Cancer Visual Aid states "In patients receiving Tarceva plus gemcitabine for pancreatic cancer, myocardial infarction/ischemia, cerebrovascular accident, and microangiopathic hemolytic anemia with thrombocytopenia have occurred, which have included fatalities." This disclosure of these potentially fatal risks associated with Tarceva is presented under the prominent header "Extending survival for moments that matter." Moreover, this presentation is difficult to distinguish from the efficacy claims due to lack of white space. In addition, the presentation on back page of the Pancreatic Cancer Visual Aid appears to be a summary of key promotional messages about Tarceva. This summary page presents bolded, prominent presentations highlighting the overall survival benefit for Tarceva plus gemcitabine, NCCN recommendation and approved indication, and the reduction in the risk of death with this regimen. However, the risk information highlight is limited to five common adverse reactions associated with Tarceva, i.e., fatigue, rash, nausea, anorexia, and diarrhea. By failing to mention any of the serious, potentially fatal risks associated with Tarceva, this presentation misleadingly suggests that Tarceva is safer than has been demonstrated by substantial evidence. We note several pages include footnotes referring the reader to the Important Safety Information (ISI) on pages 12-14 and 22-23 of the Pancreatic and NSCLC Visual Aids, respectively; however, this does not mitigate the misleading risk presentation in each of the visual aids.

Conclusion and Requested Action

For the reasons discussed above, the Pancreatic Cancer Visual Aid and the NSCLC Visual Aid misbrand Tarceva because they contain misleading efficacy claims, minimize the risks,

[8] Tarceva [package insert]. Farmingdale, NY: OSI Pharmaceuticals, LLC, an affiliate of Astellas Pharma US, Inc; 2012.

and overstate the efficacy of Tarceva in violation of the FD&C Act, 21 U.S.C 352(a). *Cf.* 21 CFR 202.1(e)(5)(i); (e)(6)(i), (xviii); (e)(7)(i), (iii), & (viii).

OPDP requests that Genentech immediately cease the dissemination of violative promotional materials for Tarceva such as those described above. Please submit a written response to this letter on or before October 18, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Tarceva that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP) and the Division of Consumer Drug Promotion (DCDP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to MA #259 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Tarceva comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Marybeth Toscano, PharmD
Regulatory Review Officer
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Office of Prescription Drug Promotion

Karen Rulli, Ph.D.
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/s/

MARYBETH TOSCANO
10/03/2012

KAREN R RULLI
10/03/2012